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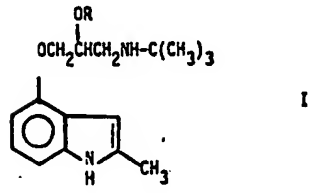
(54) Compositions containing 3-aminopropoxy-indoles for treating hypertension

(57) Pharmaceutical compositions contain:



I

wherein R is hydrogen or benzoyl,
in free form or as acid addition salt. They are suitable for the prophylaxis and therpay of ailments normally treated with β-adrenoceptor blocking agents and are adapted for administration at longer-than-daily intervals. The compositions may further contain a diuretic e.g. chlorthalidone or indapamide etc.

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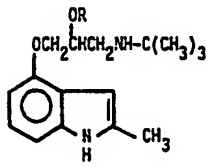
SPECIFICATION

Pharmaceutical compositions comprising 3-aminopropoxy-indoles optionally in combination with a diuretic, and their use

The present invention relates to 3-aminopropoxy-indoles.

In particular, the invention relates to compounds of formula I



I

wherein R is hydrogen or benzoyl,

in free form or in pharmaceutically acceptable acid addition salt form.

R preferably is benzoyl. The corresponding compound of formula I is known under the generic name bopindolol.

The compounds of formula I and their salts are potent β-adrenoceptor blocking agents. They are known per se from e.g. BE 734 126 and DOS 2635209.

It is well-known that β-adrenoceptor blocking agents are suitable for the prophylaxis and treatment of e.g. cardiovascular disturbances such as hypertension, arrhythmias and angina pectoris. Administration of such agents, e.g. orally, is usually effected several times a day owing to their limited duration of activity. Thus propranolol is normally administered orally in dosages of about 80 mg to about 480 mg per day, given twice daily, when used in hypertension; and of about 10 mg to about 160 mg per day, given 3 or 4 times daily, when used in angina pectoris; and in other indications such as arrhythmia, migraine, etc., oral administration is also normally effected several times a day (*Modern Drug Encyclopedia and Therapeutic Index*, A.J. Lewis, Ed., Yorke Medical books, 1981, page 824). For pindolol the oral dosage may be 5 to 15 mg given as a single daily dose or 20 to 30 mg divided into 2 or 3 daily doses or given once a day, when used in hypertension; and 10 to 30 mg generally divided into 2 or 3 single doses daily or once-a-day in retard form, when used in other indications (Sandoz-Index 1984–1986, p. 149).

Similarly, it is known from e.g. BE 734 126 that the compound of formula I wherein R is hydrogen may be administered at a daily dose comprised between about 0.5 mg and about 50 mg and an Example of a tablet containing 5 mg of the compound is disclosed therein.

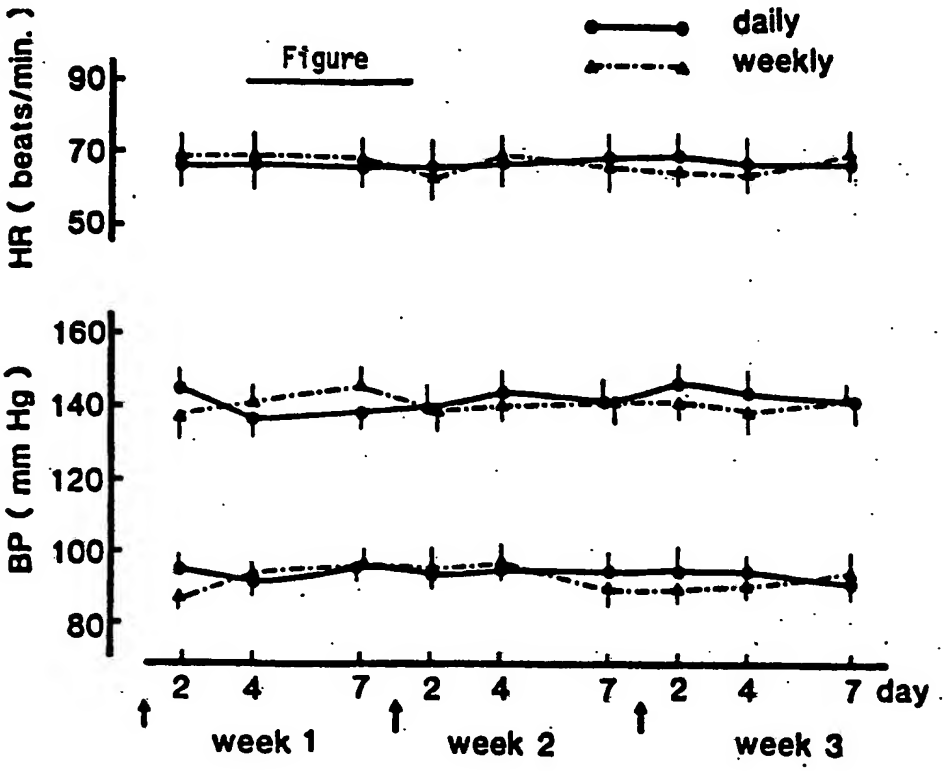
It has now been surprisingly found that the compounds of formula I in free form or in pharmaceutically acceptable salt form are suitable for administration at longer than daily intervals, e.g. every second day, or once or twice a week, even when not in sustained release form.

The exceptionally extended duration of activity of the compounds of formula I appears e.g. from the following clinical study:

Eight male patients with essential hypertension previously untreated and with diastolic blood pressure (DBP)>95–<125 mm Hg and systolic blood pressure (SBP) such that mean arterial pressure (MAP) was >117 mm Hg for the age 30–39 and >127 mm Hg for the age 40–65 years were selected for the study. The mean age was 54 years (range 35–63) and the mean weight 87 kg (range 67.1–114). The study was within the long-term testing of bopindolol and was designed as a 6-weeks double blind comparison of 1 mg bopindolol once daily v.s. 8 mg once weekly. Blood pressure (SBP and DBP) and heart rate (HR) were measured after 10 min. supine rest and 2 min. in the standing position. The trial preparations were given in the morning in 3-weeks periods as capsules containing either 1 mg of bopindolol taken daily or 8 mg of bopindolol at the start of the week followed by placebo capsules.

Routine methods were used for calculation of means ±SEM. Statistical significances of differences from values obtained at placebo treatment were calculated by analysis of variance followed by Student's t-test. Differences were regarded as significant when $p<0.05$.

When comparing sitting BP and HR measured on different dose regimens, it is obvious (Fig.) that during therapy with bopindolol 8 mg once weekly the BP level is well maintained in comparison with the results on 1 mg daily. The BP at the ends of the three treatment weeks were 146±5/97±4, 141±6/90±5 and 143±7/96±5 mm Hg when bopindolol was taken as an 8 mg dose at the start of each week. Corresponding BP:s were 139±5/97±4, 142±6/95±5 and 143±4/92±4 mm Hg when bopindolol was administered as 1 mg daily. No significant differences regarding HR were observed (Fig.).



Sitting blood pressure (BP) and heart rate (HR) during treatment with bopindolol 1 mg daily or 8 mg weekly (tablet intake indicated by arrows). Shown are means±SEM of SBP, DBP and HR (n=8).

Few and only well-tolerated side effects were observed. The frequency of side effects was not different during placebo therapy.

The results from the comparison of once daily dosage vs once weekly dosage show that a single weekly dose which is well tolerated and which does not cause undue reductions of heart rate and blood pressure during peak effect is able to maintain blood pressure control.

This unexpected, exceptional tolerability allows a full weekly dosage to be given in one single shot, or in two half-weekly shots. Further, overdosage through mistaken administration at short intervalls is unlikely.

Administration of a compound of formula I is thus possible at longer-than-daily intervalls, e.g. every second day or once or twice weekly.

This finding is very surprising. Indeed, β-adrenoceptor blocking agents such as propranolol or timolol are usually effective for a few hours only and thus need to be administered at least once or twice a day, or to be in sustained release form. However, even sustained release forms can only extend the duration of the effect to a limited extent, usually to up to 24 hours, since they are only effective at best for as long as it requires for the formulation to pass through the gastro-intestinal tract. Further they are expensive and difficult to produce and it is not easy to attain constant plasma levels.

Only recently have β-adrenoceptor blocking agents been developed, e.g. nadolol, that have an activity of their own extending over about 24 hours. The possibility that an antihyptertensive drug with an activity extending over a longer period might be used in a form allowing administration at even less frequent intervalls, i.e. once or twice weekly, seems not to have been considered at all by the specialist world.

The above finding clearly has far-reaching implications. For example, if young people with mild hypertension are to be subjected to life-long therapy, compliance may well be dramatically improved even over once daily treatment. Additionally, no sustained release formulation is necessary, thereby reducing the influence of interpatient variability, e.g. diet-related, or related to gastro-intestinal function, on the pharmacokinetic properties of the formulation.

The invention thus provides pharmaceutical compositions adapted for administration at longer-than-daily intervals in cardiovascular medication, hereafter referred to as "the compositions of the invention", comprising a compound of formula I as defined above, in free form or in pharmaceutically acceptable salt form.

The compositions of the invention make possible a novel approach to the prophylaxis and therapy of ailments commonly treated with β-adrenoceptor blocking agents, in particular cardiovascular disturbances such as hypertension.

For the above-mentioned uses the exact dosage will, of course, vary depending on the compound employed, mode of administration and treatment desired. However, in general, satisfactory results may be obtained when administered at a weekly dosage of from about 0.05 mg/kg to about 0.5 mg per kg animal body weight, conveniently given in divided doses 1 to 4 times a week or in sustained release form if even further prolongation of the duration of activity is desired. For the larger mammal the total weekly dosage is in the range of from about 4 mg to about 32 mg, and dosage forms suitable for oral or non-oral administration comprise from about 1 mg to about 32 mg of the compounds admixed with a solid or liquid pharmaceutical carrier or diluent. An example of a weekly dosage is from about 4 mg to about 16 mg. Preferred is a weekly dosage of from about 4 mg to about 10 mg, especially of from about 4 mg to about 8 mg. For twice-weekly administration the above dosages are reduced by one half, i.e. for the larger mammal the total twice-weekly dosage is from about 2 mg to about 16 mg. An example of a twice-weekly dosage is from about 2 mg to about 5 mg, especially from about 2 mg to about 4 mg.

Preferred is the compound of formula I wherein R is benzoyl.

The compositions of the invention may be administered with the compounds of formula I in free form or in pharmaceutically acceptable salt form, preferably acid addition salt form, e.g. hydrogen malonate salt form, in association with a pharmaceutical carrier or diluent. Such salt forms exhibit the same order of activity as the free forms and are readily prepared in conventional manner.

The compositions of the invention may be in the form of, for example, a capsule, a transdermal patch or a tablet. Oral or transdermal administration is preferred.

The present invention also provides a method for the prophylaxis and therapy of ailments commonly treated with β-adrenoceptor blocking agents, comprising administering to a subject in need of such treatment a composition of the invention at longer than daily intervals, e.g. every second day or once or twice weekly, preferably once weekly.

The present invention also provides for the use of a unit dosage form adapted for administration at longer-than-daily intervals in the prophylaxis and therapy of ailments commonly treated with β-adrenoceptor blocking agents, in particular cardiovascular disturbances such as hypertension, comprising from about 1 mg to about 32 mg of the compounds.

The above findings further indicate that the compounds of formula I are ideally suited for combination with a long-acting diuretic, The choice of the particular diuretic to be used is, however, not indifferent. It should clearly preferably be relatively long-acting. Several known diuretics, e.g. hydrochlorothiazide, chlorthalidone, metolazone, amiloride, indapamide, etc., have an activity over a duration exceeding 6 hours.

It has, however, now been found that two particular long-acting diuretics, namely chlorthalidone and indapamide, are particularly well-suited for combination with a compound of formula I.

Thus in a further aspect the invention provides a pharmaceutical composition comprising a compound of formula I as defined above in free form or in pharmaceutically accepted acid addition salt form and either chlorthalidone or indapamide, hereinafter referred to as "the combinations of the invention".

Chlorthalidone and indapamide are ideally suited for combination with a compound of formula I and use in hypertension. The onset of action is slow enough to avoid acute diuresis in the first 2 hours after administration but the duration of action, while being relatively long for a diuretic, is nonetheless short enough to avoid disturbing diuresis during the night.

The two active agents preferably are in a fixed combination. Here again, the compatibility of the active agents is surprisingly good. Indeed, development of a fixed combination is never a trivial matter, particularly in the antihypertensive field, which by its very nature concerns a large, very heterogenous population of patients. Patients metabolize the active components with differential speed, thereby the proportions of the components are continuously varying. As a consequence the intensity of the therapeutic activity is also continuously varying and it is therefore important to select components having compatible pharmacodynamic profiles as regards factors such as first-pass effect in the liver, etc.

Bopindolol is preferred as the β-blocker. Chlorthalidone is preferred as the diuretic. Administration of the composition with both active agents may be effected e.g. on a once-daily basis or at longer intervals, e.g. every second day or once or twice weekly, preferably on a once-daily basis.

The compound of formula I may be in free form or in salt form in the combination, e.g. as hydrochloride, fumarate, hydrogen malonate, etc., preferably as hydrogen malonate.

Exceptionally few side effects are observed with the combination when this is used in antihypertensive therapy. No orthostatic hypotension is observed and the usual accompanying symptoms normally associated with antihypertensive therapy such as dizziness, headache, buzzing in

the ears, general lassitude, etc. are minimal. The antihypertensive activity is surprisingly long-lasting.

Although it is well-known that β-adrenergic blocking agents reduce the blood pressure of an antihypertensive subject it was not to be expected that the combinations of the invention would possess such a favourable activity.

The invention also comprises a pharmaceutical composition containing a combination of the invention, suitable for enteral or parenteral administration, e.g. tablets, dragees, etc., preferably tablets. For the preparation of such compositions the combination is worked up with conventional organic or anorganic, pharmacologically inert adjuncts; for example lactose, starch, polyvinylpyrrolidone, stearic acid, sorbic acid, talc, methyl cellulose, alcohols, glycerine, etc. may be used. Further the compositions may contain appropriate sweetening or colouring agents, flavouring agents, etc.

For the above-mentioned use in combination with chlorthalidone or indapamide the exact dosage will, of course, vary depending on the compound employed, mode of administration and treatment desired. However, in general, satisfactory results may be obtained when the β-adrenoceptor blocking agent is administered at a dosage corresponding to a daily dosage of from about 0.1 mg to about 2 mg, preferably of from about 0.5 mg to about 1 mg, in combination with a dosage corresponding, for the diuretics, to a daily dosage of from about 1 mg to about 50 mg; for chlorthalidone, preferably of from about 2.5 mg to about 50 mg, preferably from about 10 mg to about 50 mg, especially from about 12.5 mg to about 25 mg; for indapamide, preferably of from about 1 mg to about 5 mg, especially from about 1 mg to about 2 mg of the diuretics.

Administration preferably is effected in the morning.

The two active agents are thus normally present in a weight ratio of β-adrenoceptor blocker to diuretics of from about 1:500 to about 2:1, preferably of from about 1:100 to about 1:1; more specifically, for chlorthalidone, preferably of from about 1:500 to about 1:1.25, especially of from about 1:500 to about 1:5, more especially of from about 1:250 to about 1:6.25, particularly about 1:20; for indapamide, especially of from about 1:50 to about 2:1, preferably of from about 1:20 to about 2:1, especially of about 1:2.

The following Examples illustrate the invention:

A) *Administration of a single active agent at weekly or twice weekly intervals in cardiovascular medication*

Example 1: Composition adapted for administration at weekly intervals in cardiovascular medication

Hard gelatine capsule containing:	mg
Bopindolol (hydrogen malonate) (= 8 mg base)	10.184
Lactose	191.066
Corn starch	140.0
Silica (Aerosil® 200, Degussa)	1.75
Stearic acid	7.0
	350.0

Example 2: Composition adapted for administration at weekly intervals in cardiovascular medication

Tablet containing:	mg
Bopindolol (hydrogen malonate) (= 10 mg base)	12.73
Lactose	91.55
Corn starch	12.8
Hydroxypropylmethylcellulose (Pharmacoat 603®, Shinetsu)	6.5
Iron oxide red	0.055
Malonic acid	0.21
Ricinoil hydrogenated (Cutina HR®)	1.95
Sodium carboxymethyl starch (Primojel®)	4.2
Tablet diameter: 9 mm	130.0

Examples 3 and 4: Compositions adapted for administration at weekly or twice-weekly intervals in cardiovascular medication

Tablet containing:	Example 3 (weekly) (mg)	Example 4 (twice-weekly) (mg)
Bopindolol (hydrogen malonate) (= 10 or 5 mg base)	10.184	5.092
Lactose	166.29	147.306
Corn starch	22.0	19.0
Hydroxypropylmethyl cellulose (Pharmacoat 603®, Shinetsu)	11.0	9.5
Iron oxide red	0.0906	0.08
Malonic acid	0.0254	0.022
Ricinoil hydrogenated (Curtina HR®)	3.3	2.85
Sodium carboxymethyl starch (Primojel®)	7.11	6.15
total	220	190
Tablet diameter:	9 mm	8 mm

Examples 5 to 8: Compositions adapted for administration in cardiovascular medication

Hard gelatine capsule containing:
the ingredients mentioned in Examples 1 to 4, respectively, with the exception that bopindolol is replaced by an equivalent amount on a molar basis of 4-(3-tert-butylamino-2-hydroxypropoxy)-2-methylindole (compound of formula I wherein R is hydrogen) in hydrogen malonate form.

B) *Administration of a combination of two active agents:*
Examples 9 and 10: Compositions for administration e.g. once a day in hypertension

Tablet containing:	Example 9 (mg)	Example 10 (mg)
Lactose (200-mesh)	130.61	118.11
Hydroxypropylmethyl cellulose	9.00	9.00
Corn starch	18.00	18.00
Bopindolol (hydrogen malonate (= 1 mg base)	1.273	1.273
Chlorthalidone (free form)	12.50	25.0
Iron oxide (red)	0.076	0.076
Malonic acid	0.021	0.021
Ricinus oil hydrogenated (Cutina HR®)	2.70	2.70
Sodium carboxymethyl starch	5.82	5.82
total	180.00	180.00
Tablet diameter: 8 mm		

Example 11: Composition for administration e.g. once-a-day in hypertension

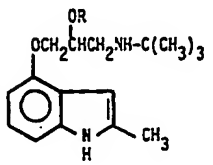
Tablet containing:	mg
Lactose (200-mesh)	140.61
Hydroxypropylmethyl cellulose	9.00
Corn starch	18.00
Bopindolol (hydrogen malonate) (= 1 mg base)	1.273
Indapamide (free form)	2.50
Iron oxide (red)	0.076
Malonic acid	0.021
Ricinus oil hydrogenated (Cutina HR®)	2.70
Sodium carboxymethyl starch	5.82
Tablet diameter: 8 mm total	180.00

Examples 12, 13 and 14: Compositions for administration e.g. once a day in hypertension

Tablet containing:
the ingredients indicated in Examples 9, 10 and 11, respectively, wherein bopindolol is replaced by an equivalent amount on a molar basis of 4-(3-tert-butylamino-2-hydroxypropoxy)-2-methyl-indol in hydrogen malonate form (i.e. an amount corresponding to 0.76 mg free base).

CLAIMS

1. A pharmaceutical composition adapted for administration at longer-than-daily intervals in cardiovascular medication comprising a compound of formula I



I

wherein R is hydrogen or benzoyl,
in free form or in pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

2. A composition according to claim 1 for the prophylaxis or therapy of ailments commonly treated with β-adrenoceptor blocking agents.

3. A composition according to claim 2 for the prophylaxis or therapy of angina pectoris,

arrhythmias or hypertension.

4. A composition according to claim 1 in unit dosage form comprising per unit dosage form 1 mg to 32 mg of a compound of formula 1 as defined in claim 1, in free form or in pharmaceutically acceptable acid addition salt form.

5. A composition according to claim 4 comprising per unit dosage form 4 mg to 16 mg.

6. A composition according to claim 1 comprising the compound of formula 1 wherein R is benzoyl.

7. A composition according to claim 1 comprising the compound of formula I wherein R is hydrogen.

8. A composition according to claim 1 for administration once a week.

9. A composition according to claim 1 for administration twice a week.

10. A composition according to claim 1 for administration every second day.

11. A unit dosage form adapted for administration at longer-than-daily intervals in cardiovascular medication containing per unit dosage form 1 mg to 32 mg of a compound of formula I as defined in claim 1, in free base form or in pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent.

12. A unit dosage form according to claim 11 containing 4 mg to 8 mg of a compound of formula I.

13. A pharmaceutical composition comprising

a) a β-adrenoceptor blocking agent of formula I as defined in claim 1 and

b) a diuretics selected from chlorthalidone and indapamide, in free form or in pharmaceutically acceptable acid addition salt form.

14. A composition of claim 13 comprising bopindolol as a β-adrenoceptor blocking agent.

15. A composition of claim 13 or 14 comprising chlorthalidone as a diuretics.

16. A composition of claim 13 or 14 comprising indapamide as a diuretics.

17. A composition of claim 13 comprising 0.1 mg to 2 mg of component a) and 1 mg to 50 mg of component b).

18. A composition of claim 13 comprising 0.5 mg to 1 mg of component a) and 1 mg to 50 mg of component b).

19. A composition of claim 13 for use against hypertension.

20. A process for the preparation of a composition of claim 13 comprising mixing components a) and b) together and if desired with pharmaceutically acceptable carriers or diluents.

21. A composition of claim 13 wherein the two active agents are present in a weight ratio of component a) to component b) of from about 1: 500 to about 2:1.

22. A composition of claim 13 wherein the two active agents are present in a weight ratio of from about 1: 100 to about 1:1.

23. A composition of claim 13 wherein the two active agents are present in a weight ratio of component a) to chlorthalidone of from about 1:500 to about 1: 1.25.

24. A composition of claim 13 wherein the two active agents are present in a weight ratio of component a) to chlorthalidone of from about 1:500 to about 1:5.

25. A composition of claim 13 wherein the two active agents are present in a weight ratio of component a) to chlorthalidone of from about 1:250 to about 1: 6.25.

26. A composition of claim 13 wherein the two active agents are present in a weight ratio of component a) to chlorthalidone of about 1:20.

27. A composition of claim 13 wherein the two active agents are present in a weight ratio of component a) to indapamide of from about 1:50 to about 2:1.

28. A composition of claim 13 wherein the two active agents are present in a weight ratio of component a) to indapamide of from about 1:20 to about 2:1.

29. A composition of claim 13 wherein the two active agents are present in a weight ratio of component a) to indapamide of about 1:2.

30. A composition of claim 13 which is a fixed composition.

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